Effects of Betahistine HCl, Nicotinic Acid, and Histamine on Basilar Blood Flow in Anesthetized Dogs

BY WESLEY D. ANDERSON, D.V.M., PH.D.,* AND WILLIAM G. KUBICEK, PH.D.†

Abstract:
Effects of Betahistine HCl, Nicotinic Acid, and Histamine on Basilar Blood Flow in Anesthetized Dogs

An intermandibular-transclival approach to the posterior cranial fossa has been developed which allows exposure of the basilar artery for attachment of a small electromagnetic blood flow transducer. The results of single intravenous injections of betahistine hydrochloride indicated a mean increase in basilar artery blood flow of 54% and a simultaneous decrease in systemic arterial blood pressure of a duration of action of approximately one minute. Histamine phosphate yielded results similar to betahistine hydrochloride, while nicotinic acid produced only slight increases in blood flow in the basilar artery.

ADDITIONAL KEY WORDS
- labyrinthine artery
- electromagnetic blood flow transducer
- basilar artery
- craniectomy
- posterior cranial fossa

The measurement of extracranial blood flow by electromagnetic blood flow transducer has been reported.1-4 On the other hand the direct measurement of intracranial blood flow in dog has been studied by only a few investigators.5,6

The present experiments were designed to directly and continuously measure basilar blood flow under the influence of vasoactive compounds in healthy anesthetized dogs.

Methods
Healthy dogs, weighing between 28 and 56 kg, were used. All dogs were randomly selected after having been treated for internal and external parasites and vaccinated against the common diseases of dog.

All animals were anesthetized with pentobarbital sodium (Nembutal), 25 mg/kg of body weight. A four-inch incision was made through the skin of the intermandibular region and the buccal cavity was entered by dissecting along the lateral surface of the tongue. Ligation of one lingual artery and unilateral section of hypoglossal and lingual nerves facilitated entrance into the buccal cavity. The body of the hyoid bone was transected and the tongue retracted laterally (fig. 1). The nasopharynx was entered by longitudinally incising the soft palate. An area of mucosa of the dorsal surface of the nasopharynx was removed from the peristeum of the basisphenoid and basioccipital bones, and craniectomy was performed directly over the origin of the labyrinthine arteries using a high-speed dental drill (fig. 2). A bone segment approximately 2.0 x 0.5 cm was removed and the dura mater was incised and retracted. The arachnoid was partially stripped from a portion of the basilar artery to enable application of an electromagnetic blood flow transducer with internal diameter of 0.75-1.0 mm. Special care was taken to keep the disturbance for 30 minutes or more following placement of the transducer around the artery; this allowed time for the two electrodes within the transducer to become firmly seated against the artery wall in systole and diastole. Basilar blood flow was measured in this manner in 15 experiments (fig. 3).

Blood pressure was measured from the femoral artery with an indwelling catheter attached to a Statham physiological pressure...
transducer (P23AA). The output from the transducer passed through an amplifier* to a Honeywell model 1108 visicorder.† The Statham pressure transducer and catheter system were filled with a dilute heparin solution (0.01% heparin solution 1,000 units/ml), and frequent flushing assured patency of the system.

The dorsal branch of the medial saphenous vein was catheterized for injection of vasoactive compounds. Betahistine HCl powder was dissolved in ethanol or normal saline solution and injected slowly into the intravenous catheter and further diluted by flushing the catheter with saline. A slow continuous infusion of saline was used throughout the experiment to maintain patency of the catheter.

To obtain zero flow measurements for the purpose of establishing baseline recordings, the basilar artery was temporarily occluded distal to the transducer with plastic-tipped forceps.

Since the electromagnetic blood flowmeter has a linear response to flow, the transducer was not calibrated in absolute flow but rather the ratio of deflection, obtained under control condition as compared to maximum change induced by the vasoactive compounds, was used.

The vasoactive compounds, betahistine hydrochloride (Serc)‡ in dose levels of 0.055 to 0.44 mg/kg, histamine phosphate 0.012 to 0.025 mg/kg, and nicotinic acid (Niacin) 1.1 mg/kg body weight, were injected intravenously. The duration of the injection of each drug was about two seconds.

* Biotronex Laboratories, Silver Springs, Maryland.
† Honeywell Inc., Minneapolis, Minnesota.
‡ Unimed Inc., Morristown, N. J.

FIGURE 1
Surgical approach to basilar artery and labyrinthine arteries in dog.
RESULTS

 EFFECTS OF BETAHISTINE HYDROCHLORIDE UPON BLOOD FLOW IN THE BASILAR ARTERY

In nine experiments blood flow was measured in the basilar artery in the control state and following injection of betahistine hydrochloride. Dose levels ranging from 0.055-0.44 mg/kg body weight injected intravenously effected increases in basilar arterial flow and decreases in femoral arterial blood pressure. The increase in basilar flow and decrease in systemic arterial blood pressure indicated vasodilation in the microcirculation of the brain had occurred approximately 20 seconds after completion of the intravenous injection of betahistine hydrochloride. The duration of effect was approximately one minute (fig. 4).
An example of individual experiment plots (fig. 5) indicates that marked increases in basilar blood flow occurred when dose levels of betahistine HCl ranging from 0.011-0.44 mg/kg body weight were injected intravenously. Volumes of the carrier solvent (normal saline or ethanol) equal to that present in the largest dose level (0.44 mg/kg) were also injected in each experiment. No change in basilar blood flow resulted following the injection of normal saline or ethanol.

In all nine experiments, betahistine hydrochloride effected an increase in basilar arterial flow ranging from 114% to 208% of the control with a mean increase of 154% of control. The mean femoral blood pressure during the period of increased basilar flow was 77% of control (fig. 6).

**EFFECTS OF BETAHISTINE HYDROCHLORIDE, HISTAMINE PHOSPHATE AND NICOTINIC ACID UPON BLOOD FLOW IN THE BASILAR ARTERY**

In six experiments (fig. 7), basilar blood flow was measured following intravenous injection of histamine phosphate, nicotinic acid and betahistine hydrochloride. Histamine phosphate, a drug with peripheral vasodilator
properties\textsuperscript{7-9} when injected intravenously in dose levels corresponding to the same molar and one-half molar equivalent dose levels as betahistine hydrochloride, produced a mean increase in basilar blood flow of 145\% of control with a standard error of the mean of ±16.274.

Nicotinic acid injected in a dose level of 1.1\ mg/kg 30 minutes later resulted in only a slight increase in basilar blood flow of 109\% of control. The standard error of the mean was ±1.759.

Betahistine HCl caused increases in basilar blood flow ranging from a low of 114\% of control to a high of 200\% of control with a mean increase of 151\% of control. The standard error of the mean was ±12.668 (fig. 7).

**Discussion**

Some are of the opinion, as recently recorded by Toole and Patel,\textsuperscript{10} that many drugs marketed today as cerebral vasodilators (e.g., nicotinic acid, pentylenetetrazol, and histamine) may produce such profound systemic vasodilatory changes that the net result may be local or generalized reduction in cerebral perfusion and flow.

In our experience, the compounds betahistine hydrochloride and histamine phosphate produced considerable increases in basilar blood flow as well as a decrease in femoral arterial blood pressure in dogs when injected intravenously and measured with an electromagnetic flow transducer. On the other hand, nicotinic acid appeared to have only slight effect on basilar blood flow. Our results compare with those of Scheinberg,\textsuperscript{11} who used the nitrous oxide procedure to measure cerebral blood flow in normal human subjects and patients with various disease states and also found little change in cerebral blood flow following administration of nicotinic acid. Carotid sinus reflex or reactive hyperemia appeared to play no significant role in the blood flow changes observed in these experiments. The small differences between the time of onset of the blood pressure changes and the blood flow changes were probably due to transit and reaction time differences to the various sites of action.
Normalized Blood Flow and Pressure in Basilar Artery of Dog
Treated with Betahistine Hydrochloride (Serc)

FIGURE 5
Increases in basilar arterial flow and decreases in femoral arterial blood pressure following intravenous injection of betahistine hydrochloride. Volumes of the carrier solvent (normal saline or ethanol) equal to that present in the largest dose level were injected in each experiment.

Acknowledgment
We wish to thank Dr. Robert Johnson and Dr. William Shimp for assisting with the experiments, and Mr. Robert Patterson, Mr. David Witsoe and Mr. Larry Stradal, who rendered valuable technical assistance. Mr. Phillip Ewing and Miss Barbara Ristuben, R. N., are also to be thanked for their help with the experiments and processing the data.

References

Effects of Betahistine Hydrochloride on Basilar Blood Flow and Femoral Arterial Pressure in Nine Experiments

FIGURE 6
Mean changes (± SEM) in basilar flow and femoral arterial pressure following intravenous injection of betahistine hydrochloride in the anesthetized dog.
Effects of Betahistine Hydrochloride (Serc), Histamine and Nicotinic Acid (Niacin) on Normalized Basilar Blood Flow and Femoral Arterial Pressure

Mean changes (± SEM) in basilar blood flow in six experiments in anesthetized dog following intravenous injection of betahistine hydrochloride (Serc), histamine phosphate and nicotinic acid (Niacin).

Effects of Betahistine HCl, Nicotinic Acid, and Histamine on Basilar Blood Flow in Anesthetized Dogs
WESLEY D. ANDERSON and WILLIAM G. KUBICEK

Stroke. 1971;2:409-415
doi: 10.1161/01.STR.2.4.409

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/2/4/409

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/